## Remarks

The undersigned requested an interview with the Examiner at the time of filing the Response filed on March 30, 2009 if the Examiner did not believe that the claims were in condition for allowance. Instead of calling the undersigned, the Examiner issued a fourth Office Action.

Applicants have set forth detailed arguments in previous responses and below, explaining why the claims are novel and non-obvious over the prior art. Applicants also address below the Examiner's rejections under 35 U.S.C. § 112.

Applicants believe that the claims should be in condition for allowance. However, if the Examiner believes that any issues remain to prevent the allowance of the claims, Applicants respectfully request an interview with the Examiner to expedite allowance of this application.

## Rejection Under 35 U.S.C. § 112, second paragraph

Claim 12 [*sic*] was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner indicated that claim 12 recites "that the gradient is suitable for analysis." However, this limitation is not present in claim 12. Therefore, Applicants respectfully traverse this rejection.

Although no rejection of claim 18 has been formally made, Applicants amended claim 18 in view of the Examiner's comments in the rejection under 35 U.S.C. § 112, second paragraph, to expedite allowance of this application. Claim 18 as amended depends from claim 13, and

further defines the method of analysis. Support for this amendment can be found in the specification at least at page 7, lines 20-26.

**Rejection Under 35 U.S.C. § 112, first paragraph**

Claims 1-4 and 7-12 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully traverse this rejection.

**Legal Standard**

The general standard for the written description requirement is that "a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." *See* M.P.E.P. § 2163(I).

**Analysis**

The Examiner acknowledged that the application as originally filed discloses "exposing the substrate to the first solution itself." Office Action, page 3, first para. However, the Examiner objected to the limitation in claim 1 of "exposing the substrate to the advancing front of a first solution". *Id.* Contrary to the Examiner's assertion, the specification does describe exposing the substrate to an advancing front. For example, at page 2, lines 20-22, the specification discloses "moving a liquid boundary in relative motion to the substrate surface". Further, claim 1 as originally filed specifies the step of "exposing the substrate to an advancing front of a first solution comprising a first adsorbate." With respect to original claims, the

M.P.E.P. states that "there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed." M.P.E.P. § 2163(I) (A), *citing In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976). One of ordinary skill in the art would reasonably conclude that Applicants were in possession of the method defined by claim 1 and its dependent claims based on the disclosure in the specification and claims as originally filed, Therefore claims 1-4 and 7-12 meet the written description requirement.

**Rejection Under 35 U.S.C. § 102**

Claims 1, 2, 4, 7, 10, 12, 13, and 16-18 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 6,242,264 to Natan *et al.* ("Natan"). Applicants respectfully traverse this rejection.

***The Claims***

The claims define methods for preparing chemical gradients on the surface of a substrate, radially symmetric chemical gradients and methods of using such chemical gradients. Claim 1 has been amended to clarify that the speed at which the substrate is be exposed to an advancing front of a first solution comprising a first adsorbate is selected based on the adsorption kinetics of the first adsorbate onto the surface of the substrate. Support for this amendment can be found in the specification at least at page 4, lines 9-13 and page 5, lines 3-7.

***Chemical Gradients are Different from Morphological Gradients***

Surface chemical gradients and surface morphological gradients are used to as research tools for cost-effective analysis of the influence of a wide range of parameters in a minimum

amount of time. Morgenthaler, *et al.*, "Surface-chemical and -morphological gradients", *Soft Matter*, 4:419-434, 419, left col. (2008) (herein "Morgenthaler 2008", a copy of which is enclosed).

Chemical gradients and morphological gradients are different types of gradients with different properties and are formed using different processes.

Surface chemical gradients are gradual changes in the chemistry of a surface. This affects various physical properties associated with the surface, such as wettability. *See e.g.*, Ruardy, T.G., et al., *Surf. Sci. Rep.* **1997**, *29*, 1–30 (a copy of which was provided with the Information Disclosure Statement filed July 16, 2004) "[c]hemical gradient surfaces are surfaces with gradually changing chemistry along their length which is responsible for a position bound variation in physical properties, most notably, the wettability." Ruardy, Abstract. A surface chemical gradient does not modify that shape, or morphology, of the surface. Thus, when a flat substrate with a smooth surface is modified to contain a surface chemical gradient, the outermost surface remains flat and smooth.

In contrast to chemical gradients, morphological gradients are gradual changes is a physical structure of the surface, such as roughness or porosity, which also affect the properties of the surface. Thus, when a flat substrate with a smooth surface is modified to contain a morphological gradient, the shape of the surface is modified such that it contains rougher and smoother areas, more porous and less porous areas, higher and lower areas (e.g. varying

thicknesses), and/or areas of more concentrated particle attachment and areas with less concentrated particle attachment.

Morgenthaler 2008 describes different methods for making chemical gradients and morphological gradients and different uses for these gradients.

Standard procedures for forming chemical gradients include irradiation or chemical etching to gradually modify the outermost surface layer of a substrate and attaching a surface coating, such as a self-assembled monolayer, to the surface. Morgenthaler 2008, p. 419, right col. The present application describes a method for making chemical gradients using self-assembled monolayers created by an immersion process. This method is briefly described in Morgenthaler 2008 in the paragraph bridging pages 422 and 423.

Different procedures for forming morphological gradients include binding nanometer-sized particles onto a smooth surface (*id.*, p. 425, § 2.2.1), using electrochemical etching process to create a porosity gradient on a surface (*id.*, p. 425, § 2.2.2), polishing a rough surface to create a roughness gradient (*id.*, p. 426, § 2.2.3), by applying a mixture of two polymers to a substrate with a temperature gradient to form a two-dimensional gradient of feature size and distribution, and/or a thickness gradient (*id.*, p. 426, § 2.2.4), and using photolithography (*id.*, p. 427, § 2.2.6).

***The Claimed Methods and Surface Chemical Gradients***

Independent claim 1 defines a method for preparing a surface-chemical gradient on a substrate. The method contains the following steps:

selecting a speed at which the substrate will be exposed to an advancing front of a first solution comprising a first adsorbate, wherein the speed is selected based on the adsorption kinetics of the first adsorbate onto the surface of the substrate,

exposing the substrate to the advancing front of the first solution,

wherein the substrate is exposed to the advancing front of the first solution for a time period sufficient to adsorb the first adsorbate onto the surface of the substrate in an amount decreasing in concentration from a first area on the substrate to a second area on the substrate.

Dependent claims 2-12 depend directly or indirectly from claim 1.

Independent claim 13 defines a method of using a surface-chemical gradient for biological analysis comprising exposing the surface-chemical gradient to cells. The surface-chemical gradient is radially symmetrical and comprises a first adsorbate in an amount decreasing in concentration from a first area on the substrate to a second area on the substrate and a second adsorbate in an amount increasing in concentration from the first area on the substrate to the second area on the substrate. Dependent claims 14 and 18 depend directly from claim 13.

Independent claim 16 defines a surface-chemical gradient on a surface of a substrate comprising a first adsorbate in an amount decreasing in concentration from a first area on the substrate to a second area on the substrate and a second adsorbate in an amount increasing in concentration from the first area on the substrate to the second area on the substrate, wherein the surface gradient is radially symmetrical. Dependent claim 17 depends from claim 16.

***Natan describes morphological gradients, not surface chemical gradients***

Natan discloses forming **morphology** gradients, by attaching gold and silver metal **particles** to the surface of a substrate. This is distinct from the surface **chemical** gradients or methods for forming or using surface chemical gradients.

Natan's method is used to form surfaces with "continuous or stepped gradients in the size and number density of [mixed metal particles] [...] on different regions of a single substrate." Natan, col. 40, lines 34-36. Natan discloses methods for forming self-assembled metal colloid monolayers on organic substrates. *See e.g.* Natan, col. 1, lines 14-15; col. 3, lines 30-32. The substrate is modified by first generating hydroxyl or oxide groups on the surface and then by polymerizing bifunctional organosilanes on the surface, which contain a functional group A that is selected for its high affinity towards noble metals. Natan, col. 3, lines 2-16. Then the polymer-derivatized substrate is immersed into a solution of colloidal metal particles and surface assembly spontaneously occurs. *Id.*

The Examiner cites col. 40, lines 49-64 of Natan in support of his rejection of claims 1, 2, 10, 12, 13, and 16-18. However, the Examiner mischaracterized Natan's disclosure. First, the colloidal metal particles are **not *adsorbed directly onto*** the surface, rather they bind to functional groups that are covalently attached to the substrate's surface. Natan, col. 40, lines 50-51; *see also* Figure 1C. This process is distinct from the claimed method, which requires (1) selecting a speed based on the adsorption kinetics of the first adsorbate onto the surface of the substrate, and (2) exposing the substrate to the advancing front of the first solution for a time period sufficient

to adsorb the first adsorbate onto the surface of the substrate in an amount decreasing in concentration from a first area on the substrate to a second area on the substrate.

The addition of gold particles to the substrate surface does not form a chemical gradient on the surface, rather it forms a morphological gradient on the surface. Natan explains this result, stating "a gradient in particle coverage is generated in the direction of immersion". Natan, col. 40, lines 56-57. Natan also describes attaching silver particles after attaching gold particles. Natan describes the results of this step as forming a surface that "exhibits a continuous variation in nanometer scale morphology as defined by particle coverage and particle size". *Id.* at lines 61-63. Thus, Natan's method is different from the claimed method and produces surface morphology gradients, not the surface chemical gradients required by the claims.

Therefore claim 1 and dependent claims 2, 4, 7, 10, 12, and 18 are novel in view of Natan.

***Natan does not disclose radially symmetrical surface chemical gradients or methods of use therefore***

Independent claim 13 defines a method of using a surface-chemical gradient for biological analysis where the surface gradient is radially symmetrical. Independent claim 16 defines a radially symmetrical surface-chemical gradient on a surface of a substrate comprising a first adsorbate and a second adsorbate.

As noted above, Natan disclosed morphological gradients containing different concentrations and different sized gold or silver particles. Further, contrary to the Examiner's

assertion at page 4, section 13 of the Office Action mailed July 1, 2009, the use of a motorized translation stage does not produce a radially symmetric gradient. Rather it produces a linear gradient. Radially symmetric gradients are described in the specification at least at page 5, lines 2-8. As disclosed in the specification, radially symmetric gradients may be formed using a syringe pump, not a linear motion drive.

Therefore claims 13, 16 and 17 are novel in view of Natan.

**Rejection Under 35 U.S.C. § 103**

Claims 3, 8 and 15 were rejected under 35 U.S.C. § 103(a) as being obvious over Natan, in view of U.S. Patent No. 6,770,323 to Genzer, *et al.* ("Genzer"). Claim 11 was rejected under 35 U.S.C. § 103(a) as being obvious over Natan, in view of U.S. Patent No. 5,656,034 to Kochersperger, *et al.* ("Kochersperger"). Applicants respectfully traverse these rejections.

***Natan***

Natan discloses morphological gradients and methods for making morphological gradients, as discussed above.

***The combination of Natan with Genzer***

Genzer was previously discussed at length in the Amendment and Response filed February 4, 2008. Therefore, Applicants are only highlighting a portion of the differences between Genzer and the claims in this response.

Genzer focuses on vapor deposition methods. Further, Genzer generally teaches away from using liquids to form chemical gradients, noting that prior techniques "are typically rather

cumbersome and involve various 'wet chemistry' surface treatments, which is [*sic*] often times hard to control and not applicable to all materials." Genzer, col. 1, lines 59-62. Genzer explains that its goal is to "develop methods that would both eliminate the 'wet chemistry' environment and produce surfaces with reproducible and tunable surface properties." Genzer, col. 1, lines 62-65.

With respect to using liquids in the method for forming a surface gradient, in one embodiment, Genzer uses a liquid bath that contains a liquid concentration gradient. The only disclosure possibly relating to an advancing front is the mention of "dipping in a liquid bath" at col. 14, line 37. However, Genzer does not disclose the rate at which the substrate is dipped into the bath. Since Genzer is merely exposing the substrate to a liquid source having a fluid concentration gradient for the purpose of creating a substrate with the same concentration gradient, the entire substrate would likely be in contact with the liquid source for essentially the same time period to allow the component to deposit on the surface of the substrate in a concentration gradient that corresponds with the fluid concentration gradient in the liquid bath.

As noted above, Natan focuses on the formation of morphological gradients, not chemical gradients. Natan requires the binding of metal particles to its surface to form the morphological gradients. Therefore one of ordinary skill in the art who was practicing the methods of Natan would not look to Genzer to modify Natan's methods.

Further, neither Natan nor Genzer disclose or make obvious the step of "exposing the substrate to the advancing front of the first solution, wherein the substrate is exposed to the

advancing front of the first solution for a time period sufficient to adsorb the first adsorbate onto the surface of the substrate in an amount decreasing in concentration from a first area on the substrate to a second area on the substrate", as required by independent claim 1 and its dependent claims.

Therefore, dependent claims 3 and 8 are nonobvious over Natan in combination with Genzer.

***Claim 15 is non-obvious over Natan in combination with Genzer***

Independent claim 15 defines a method of using a surface-chemical gradient for analysis comprising exposing the surface-chemical gradient to a molecule, wherein the surface-chemical gradient comprises a first adsorbate in an amount decreasing in concentration from a first area on the substrate to a second area on the substrate and a second adsorbate in an amount increasing in concentration from the first area on the substrate to the second area on the substrate, wherein the surface gradient is radially symmetrical, and wherein the molecule preferentially binds with the first adsorbate.

As noted above with respect to claims 13, 16 and 17, Natan does not disclose a radially symmetric gradient. Further, Natan discloses forming morphological gradients, not surface-chemical gradients. Genzer does not disclose forming radially symmetric gradients, as required by claim 15. Therefore, claim 15 is non-obvious over Natan in combination with Genzer.

***Claim 11 is nonobvious in view of the combination of Natan with Kochersperger***

Claim 11 depends from claim 1 and specifies that the surface of the substrate is exposed to the first solution using a syringe pump.

***Natan***

Natan is discussed above.

***Kochersperger***

Kochersperger discloses a syringe pump designed for delivery of small volumes (*e.g.* 1 to 10 μl) at high pressure (Kochersperger, abstract and col. 1, lines 10-13). Kochersperger's syringe pump is designed for micro-scale separations in analytical chemistry (Kochersperger, col. 1, lines 6-13). Kochersperger does not disclose the formation of surface chemical gradients, nor the adsorption of a component onto a substrate.

As noted above, Natan focuses on the formation of morphological gradients, not chemical gradients. Natan requires the binding of metal particles to its surface to form the morphological gradients. Therefore one of ordinary skill in the art who was practicing the methods of Natan would not look to Genzer to modify Natan's methods.

Further, neither Natan nor Genzer disclose or make obvious the steps of (1) selecting a speed based on the adsorption kinetics of the first adsorbate onto the surface of the substrate, and (2) exposing the substrate to the advancing front of the first solution for a time period sufficient to adsorb the first adsorbate onto the surface of the substrate in an amount decreasing in concentration from a first area on the substrate to a second area on the substrate.

Therefore claim 11 is nonobvious over Natan in view of Kochersperger.

Allowance of claims 1-18, as amended, is respectfully solicited.

Respectfully submitted,

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